Neuroendocrine tumors: diagnostic imaging and radiopptide therapy

The E.S. Garnett lecture 2010
McMaster University
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Overview presentation

- PART 1. GENERAL INTRODUCTION
- PART 2. DIAGNOSTIC IMAGING
  - Carcinoids tumors
  - Pancreatic islet cell tumors
  - Phaeochromocytoma
  - Medullary thyroid cancer
  - Miscellaneous conditions
- PART 3. TREATMENT
  - General
  - Radiopeptide treatments

No disclosures.

I have no financial or other interests in this topic other than science and a desire to improve patient care.
PART 1. General overview

• The endocrine system
  – Glands and hormones
• The nervous system
  – Electrical impulses
• The neuroendocrine system
  – The interconnection
  – A network of glands + a diffuse system
  – A diffuse system
    • Scattered cells throughout organs
  – Secrete hormones after stimulus, e.g.
    • Insuline after glucose rise
    • Adrenaline after stress
Enterochromaffin cell

- App. 80% of total body serotonin
- Release upon different stimuli
- Involved in gut motility
Old APUD concept 1967
Amine Precursor Uptake and Decarboxylation

- Contain specific enzymes.
- 1967 Pearse. May cause tumors called ‘apudomas’
- Apudomas share histological, ultrastructural and biochemical properties
WHO Classification 2000: based on cell characteristics

• GastroEnteroPancreatic: GEP-NETs
  – 1. Neuroendocrine tumor – less malignant
  – 2. Neuroendocrine carcinoma – more malignant
  – 3. Poorly differentiated neuroendocrine carcinoma – most malignant
  – 4. mixed
  – 5. rare GEP-NETs

• Forbidden terms : carcinoid, pancreatic islet cell tumor

• Not generally accepted
Classification carcinoid

Carcinoids are tumors of the neuroendocrine cells in the gastrointestinal tract

Williams and Sandler, Lancet 1963
Classification based on site of origin

1. Carcinoids ~66%
   - With carcinoid syndrome 10%
   - Without carcinoid syndrome 90%

2. Pancreatic ETs ~33%
   - Non functioning 15-30%
   - Functioning 70-85%
     • Gastrinoma
     • Insulinoma
     • Glucagonoma
     • Somatostatin, - VIP-, CRH-, GHRH-, ACTH-, GRFoma

3. Rare GEP-NETs
Rare GEP-NETs

- Medullary thyroid carcinoma
- Merkel cell cancer
- Small cell lung cancer
- NE carcinoma of the lung, extrapulmonary, cervix
- Multiple Endocrine Neoplasia types 1 and 2
- Von Hippel Lindau disease
- Neuroblastoma
- Pheochromocytoma
- Paraganglioma
- Anterior pituitary tumors
- Carney’s complex
Hormones

- **Amines**
  - Serotonin
  - Histamine
  - catecholamines

- **Peptides**
  - ACTH
  - Bradykinins
  - Chromogranins
  - Somatostatin

- **Steroids**

Nearly all NE tumors have receptors for somatostatin
Biogenic amines: biosynthesis

- **Histidine**
  - Conversion to **Histamine** via histidine decarboxylase and PLP.

- **Tryptophan**
  - Converted to **Tetrahydrobiopterin**.
  - Hydroxylation to **5-Hydroxytryptophan**.
  - Decarboxylation to **Serotonin**.

- **Tyrosine**
  - Hydroxylation to **Dopa**.
  - Decarboxylation to **Dopamine**.
  - Further metabolism to **Norepinephrine** and **Epinephrine**.
Serotonin: neurotransmitter, modulator and hormone

- Involved in Central nervous system
  - Sleep-wake rhythm;
  - Food intake;
  - Sexual activity;
  - Mood.

- Involved in peripheral vessel regulation
  - Vasoconstrictor

- Involved in GI tract regulation
  - Neurotransmitter
PART 2.
IMAGING
1. Carcinoid tumors

- Distribution
  - Bronchus 20 - 30%
  - Small intestine 20 – 50 %
  - Rectum 10 %
  - Rare
    - Thymic,
    - Gastric
    - Duodenal

- Autopsy studies 75% small intestine
Bronchial carcinoid tumors

- Large cell, small cell, typical, atypical
- Symptoms
  - Bronchial obstruction, ACTH production
- CT standard
  - Round, oval, calcification
- Octreoscan
  - Sens 90%, Spec 83% also for ectopic ACTH
- Survival
  - Typical lung carcinoid 90%,
  - Atypical lung carcinoid 40%
Non ileal carcinoid tumors

- **Thymic**
  - Usually non-functioning, some ACTH
  - Anterior mediastinal mass
  - Often invasive, early metastatic
  - Poor prognosis

- **Gastric**
  - Type 1 – atrophic gastritis - gastrine - benign
  - Type 2 – thickened wall – metastasises – fairly good prognosis - MEN
  - Type 3 – no hypergastrinaemia, poor prognosis

- **Hindgut**
  - Usually slow growing
  - Better survival than other GI locations
  - Size is predictive
‘the Classic carcinoid’ – small intestine

- Most frequent NE tumor. Malignant.
- Slow growth but may be very aggressive
- Production of substances
- Symptoms
  - biogenic amines: serotonin, catecholamines….
  - Flushes and diarrhea
  - Carcinoid heart disease
  - Tumor mass effects
- Diagnosis
  - Symptoms
  - Biochemical assays –
  - Imaging
Intestinal carcinoid - US data

- Incidence 5.76 / 100,000
- Prevalence 35 / 100,000
- 5-fold increase over 30 years

- Similar to testicular cancer, myeloma, esophageal cancer – second GI tumor

- This is not a rare tumor any longer!

- However, many subtypes and much variation
- Attempt to summarize prognostic findings
Prognostic factors

Points:
- Age (years)
- Gender
- Ethnicity
- Symptoms at diagnosis
- Elevated urinary 5-HIAA
- Elevated CgA (>6× upper limit)
- Elevated liver function test
- Carcinoid heart disease
- Tumor size (cm)
- Tumor stage (SEER)
- Tumor histology (grade)
- Ki-67 index (%)
- Liver metastases
- Surgery (hepatic)
- Somatostatin therapy

Total points:
- 5-year survival (probability)
- 10-year survival (probability)

Modlin, Neuroendocrinology 2010.
‘Workup’ for patient with carcinoid tumors

- Biochemical assays
- Efficient Imaging
  - CT, ultrasound, MRI
  - Octreoscan
  - PET
- Treatments
  - Medical
    - Somatostatin analogues
    - Chemotherapy
    - New smart drugs
  - Peptide receptor radionuclide therapy
  - Curative or cytoreductive surgery, liver transplantation
  - Interventional radiology
- Treatment choice improves with better imaging
Imaging: CT scan

- Mainstay
- Little recent data on performance
- Primary tumor often not seen on CT / MR
- Mainstay for liver, lung, mesenterial metastases
- Liver mets may be iso
  - Contrast!
  - Porto-venous phase, 3 phase
- Mesenteric
  - Spoke-wheel, calcifications
Imaging: Octreo scan

- In-111-DTPA-Phe1-Octreotide
- Imaging 4, 24 and 48 p.i.
- Detects receptor positive tumors
- With CT crucial in staging
Active pathways in carcinoids provide rationale for new PET tracers

Serotonin precursor
C11-5-hydroxy-tryptophan

Catecholamine precursor
F18-DOPA

Both are amino acids
Uptake via LAT transporters
Uptake driven by AADC
Storage in vesicles
**18F-DOPA PET: a superb modality in carcinoid tumors**

- Especially in liver, bone, abdomen, pelvis

- Number of lesions/patient
  - CT 7.1
  - SRS 5.9
  - SRS + CT 8.5
  - PET 12.4
  - PET + CT 13

- Frequent unexpected findings

- Impact on management
  - 20 – 30%

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*Koopmans et al., Lancet Oncol. 2006; 7: 728-34.*
18F-DOPA PET in carcinoid tumors: excellent accuracy

Sensitivity
Using Composite Reference standard

Specificity
No FP observed Regional 100%

1 Koopmans, Jager, Lancet Oncol. 2006;7:728-34.
Unexpected findings: cardiac carcinoid metastasis
Module 1 – Administration / Clinical Information
Cover letter
Table of contents
Drug Submission application
Investigational brochure
Submission rationale
Brief summary
Prior applications
Minutes preCTA meeting
Reaction and changes from preCTA meeting
Ongoing clinical trials
Study protocol
REB – patient information
Proposed label
Supporting key paper reprints

Module 2 – Chemistry and Manufacturing Information
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Quality Information Summary: Radiopharmaceuticals
Appendix 1 – certificate of analysis
Appendix 2 – typical HPLC trace
Appendix 3 – NMR spectrum
Appendix 4 – LCMS spectrum
Appendix 5 – three batch records
Appendix 6 – SOP for synthesis of 18F-DOPA
Appendix 7 – references
Hot focus just behind pancreatic head, just in front of upper anterior rim of L3 vertebral body

Background pancreas tracer uptake is normal

R kidney tilted

Bladder

L kidney

Liver

Uptake in corpus of pancreas

Cold area is fluid filled stomach

First Canadian F-DOPA PET scan 9-1-2009
The Hamilton 18F-DOPA trial
Hamilton trial confirms European findings: excellent sensitivity and specificity

**TABLE 2 SENSITIVITY OF IMAGING MODALITIES AT PATIENT LEVEL**

<table>
<thead>
<tr>
<th></th>
<th>18F-DOPA</th>
<th>CT</th>
<th>SRS</th>
<th>SRS+CT</th>
<th>PET+CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ve in n patients of 21</td>
<td>20</td>
<td>17</td>
<td>15</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>sensitivity</td>
<td>95%</td>
<td>81%</td>
<td>76%</td>
<td>90%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Table 3 Region Based Analysis of 54 Positive Regions**

<table>
<thead>
<tr>
<th></th>
<th>PET</th>
<th>CT</th>
<th>SRS</th>
<th>CT+SRS</th>
<th>54 regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity</td>
<td>0.94</td>
<td>0.63</td>
<td>0.64</td>
<td>0.74</td>
<td>0.74</td>
</tr>
<tr>
<td>specificity</td>
<td>1.00</td>
<td>0.98</td>
<td>0.99</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

- 21 carcinoid patients – 20 positive – 9 impact on treatment
  - 2 major, 7 minor impact

- 6 patients without only suspected disease
  - Everything negative
  - One unclear liver lesion on CT, octreo and DOPA negative

- Paper in progress dr Yakemchuk
Another new PET based tool
Ga68-based - peptide PET

- Ga68-DOTA-TOC
- Ga68-DOTA-NOC
- Ga68-DOTA-Tate
**68Ga-DOTATATE** PET in negative octreoscan

**TABLE 2. Total Number of Lesions Identified in Each Type of NET with the Different Modalities**

<table>
<thead>
<tr>
<th>Site</th>
<th>Tumor grade</th>
<th>No. of patients</th>
<th>$^{111}$In-DTPA octreotide scintigraphy</th>
<th>68Ga-DOTATATE PET</th>
<th>Cross-sectional imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchus</td>
<td>Low</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1</td>
<td>0</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Low</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thymus</td>
<td>Intermediate</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Low</td>
<td>9</td>
<td>12</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Ileum</td>
<td>Low</td>
<td>12</td>
<td>7</td>
<td>40</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>10</td>
<td>3</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>Low</td>
<td>1</td>
<td>1</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1</td>
<td>0</td>
<td>12</td>
<td>12</td>
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<tr>
<td>Unknown</td>
<td>Low</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>3</td>
<td>0</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Hindgut</td>
<td>Low</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total patients</td>
<td>51*</td>
<td>27</td>
<td>168</td>
<td>226</td>
<td></td>
</tr>
</tbody>
</table>

*Includes 4 patients with no evidence of disease on cross-sectional imaging.

51 pat, 47 disease evidence, 35 neg on octreoscan, 3 all remained neg, 32 CT/MR positive, 27 PET
Sens PET 87%, spec 100%, Sensitivity decreasing with poorer differentiation Patients selected for PRRT
Ga68-peptide-PET or 18F-DOPA: depends on NET subtype


- Haug 2009: $^{68}$Ga Sens 96, vs DOPA 56% [$n=25$]
  - But 11 foregut, 5 unknown, 9 gut tumors, results not given per subgroup

- Montraverse EANM 2010:
  - in ileal carcinoid DOPA superior to Ga68-PET
Statements about Ga68-peptide-PET

- Putzer: superb in bone metastases
- Ambrosini: 50% therapy modification
- Khan: value in meningeoma planning
- Kratochwil: high uptake after intraarterial injection
- Versari: similar to EUS and CT in duodenal – pancreatic NET
- Ruf: 33% therapy change, similar to ceCT
- Kowalski: much superior to octreoscan
- Fanti: Helps in uncommon NET
- Dosimetry: 0.025 – 0.005 mSv/MBq or 1 – 5 mSv
- Sriraskanthan: finds lesions in negative octreoscan
- Kayani: better than FDG in bronchial carcinoid
- Montraverse: inferior to DOPA in ileal carcinoid
Ga68-peptide-PET: will it fly?

- Two commercial generators
- Not for human use
- Costs
- Usable for one year
- Sterility issues
- Peptide labeling issues
- Some centers sneak around this
- Netherlands: basically not possible
  - healthcare inspection has to agree, local pharmacist as to agree, pharmacy inspection has to agree, doctor has to agree per patient
- USA not FDA approved, even in Belgium difficult
- I suspect Canada will not allow for years?

**Warning**

- The IGG100 Ga-68 Generator is a chemical grade product and not intended for use in humans.
- It has not been validated as a pharmaceutical product.
2. Pancreatic islet cell tumors

- Pancreatic endocrine tumors
- (~30% of GEP-NETs)
  - Nonfunctioning (30%)
  - Functioning (70 %)
    - Producing: Gastrin, insulin, glucagon, VIP, PP, somatostatin, CRH, GHRH, ACTH, GRF, PTH

- Imaging SRS, CT
- May have very poor prognosis
  - 5 yr survival 30%
- Treatment: surgery, chemotherapy
Imaging of Islet cell tumor with CT, SRS, DOPA, HTP

CT  Octreotide  FDOPA PET  HTP PET

54 yr. patient with islet cell tumor, no tumoral hormone production.
Results: lesion based analysis (% sens)

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>SRS</th>
<th>SRS + CT</th>
<th>FDOPA</th>
<th>FDOPA + CT</th>
<th>HTP</th>
<th>HTP + CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>63</td>
<td>49</td>
<td>73</td>
<td>87</td>
<td>98</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>Islet Cell</td>
<td>68</td>
<td>46</td>
<td>77</td>
<td>41</td>
<td>80</td>
<td>68</td>
<td>96</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>48</td>
<td>75</td>
<td>66</td>
<td>90</td>
<td>74</td>
<td>92</td>
</tr>
</tbody>
</table>

PET is a superior modality, also strongly improves on CT and vice versa
Significantly better than Octreoscan

*Koopmans et al. J Clin Oncol 2008*
Carcinoid vs Pancreatic islet cell tumors

• Carcinoid patients:
  – F-DOPA PET/CT superior imaging method

• Patients with islet cell tumor:
  – HTP PET/CT best imaging method
  – CT was negative in 2 patients (FDOPA and HTP pos)
  – Octreotide in 5
  – DOPA in 6
  – HTP positive in all

• Ga68-peptide-PET likely excellent
3. Pheochromocytoma FDOPA/MIBG

24 yr patient
biochemistry positive
Recurrent malignant phaeochromocytoma. 

$^{18}$F-DOPA

- Biochemistry: positive, CT / US / MR: negative
$^{18}$F-DOPA PET showing metastases para-aortical (right)

$^{123}$I-MIBG showing physiological uptake left adrenal (incl. SPECT)
Patient based sensitivity
• DOPA 90% (vs MIBG P<0.001, CT < 0.01)
• 123I-MIBG 65%
• CT/MRI 67%

Combined PET/CT - lesion based sensitivity
• DOPA 93% (vs MIBG P<0.05, CT < 0.001)
• 123I-MIBG 76%

Conclusion
• Now many studies
• 18F-DOPA PET/CT superb modality
• Correlates with plasma metabolite activity

Fiebrich et al 2009 – JCEM 2009
4. Medullary thyroid cancer

- Rare thyroid tumor
  - 35% with mets at diagnosis
  - Sporadic and familial (MEN2)
- Curative surgery
- Frequent problem
  - Positive markers (calcitonine / CEA)
  - No substrate
- Multitude of tests
  - CT/MRI
  - $^{99m}$Tc-V-DMSA scan, $^{123}$I-MIBG, $^{99m}$Tc-MIBI,
  - $^{111}$In-octreotide, $^{123}$I-VIP, $^{111}$In-minigastrin
  - $^{18}$FDG PET, $^{18}$F-DOPA PET
\(^{18}\)F-DOPA in MTC

- Lesion based sensitivities
  - CT/MRI: 64%
  - DMSA SPECT: 19%
  - FDG PET: 30%
  - DOPA PET: 71%
  - DOPA PET/CT: 89%

- F-DOPA superior over FDG in nearly all
- In 6/8 with low calcitonine level all imaging negative
- In 2/3 with fast calcitonin doubling time was FDG superior over DOPA
### 18F-DOPA PET in MTC with increased calcitonin levels

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Sens</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoegerle</td>
<td>2001</td>
<td>11</td>
<td>63%</td>
<td>new lesions considered FP</td>
</tr>
<tr>
<td>Beuthien</td>
<td>2007</td>
<td>15</td>
<td>55%</td>
<td>retrospective,</td>
</tr>
<tr>
<td>Koopmans</td>
<td>2008</td>
<td>21</td>
<td>62-71%</td>
<td>FDG 30%, complementary</td>
</tr>
<tr>
<td>Marzola</td>
<td>2010</td>
<td>18</td>
<td>83%</td>
<td>FDG 61%, together 89% &gt; CT/MR</td>
</tr>
<tr>
<td>Behesti</td>
<td>2009</td>
<td>26</td>
<td>81%</td>
<td>FDG 58%, together 85%</td>
</tr>
<tr>
<td>Luster</td>
<td>2010</td>
<td>28</td>
<td>74%</td>
<td>Specificity 100%, with CT best</td>
</tr>
</tbody>
</table>

- Notoriously difficult patients!
- FDG may detect more dedifferentiated lesions
- DOPA detects more indolent lesions
- American Thyroid Association: calcitonin > 150 pg/mL do 18F-DOPA
- FDG and DOPA PET/CT best diagnostic modality
Until recently, identification of these foci involved catheterisation of pancreatic vessels and sampling of insulin concentrations, during which time the baby was hypoglycaemic for up to several hours. However, PET-CT scanning with an F-DOPA label (taken up by DOPA decarboxylase in the beta cells) has revolutionised this area. It generates beautifully clear images of focal and diffuse disease both non-invasively and under euglycaemic conditions. Such images allow the surgeon to accurately localise the lesion, and laparoscopic surgery for this condition is being pioneered in some centres.

Paediatric access to a PET-CT scanner may be possible elsewhere in the city, but will require considerable planning. Furthermore, F-DOPA is apparently rarer than gold dust! I have recruited the help of a consultant colleague in nuclear medicine at the Manchester Royal
TABLE 2
Clinical Applications of $^{18}$F-DOPA PET in Hyperinsulinism

<table>
<thead>
<tr>
<th>No. of patients with indicated disease form</th>
<th>No. of patients undergoing surgery</th>
<th>No. (%) of patients for whom $^{18}$F-DOPA PET results (vs. surgery) were correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>Diffuse</td>
<td>Focal</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>9 (5 with focal form + 4 with diffuse form)</td>
</tr>
</tbody>
</table>
PART 3. RADIOPEPTIDE TREATMENT
Cytoreductive therapies for inoperable neuroendocrine tumors

- Somatostatin analogues and interferon-alpha:
  - Symptomatic control, antitumor effects <10%.

- RFA, (Chemo)Embolization of liver metastases:
  - If tumorload >75% in liver, lesions <4 cm.
  - Local responses reported in 25-85%.

- Surgical debulking
- Chemotherapy:
  - Conventional
  - smart drugs / biologicals coming . . .

- Peptide Receptor Radionuclide Therapy (PRRT)

Courtesy Dik Kwekkeboom, Erasmus Medical Center, Rotterdam, The Netherlands
PRRT sites

[Map showing PRRT sites around the world]
Radiolabeled Somatostatin Analogues used for PRRT

- $[^{111}\text{In-DTPA}^0]$ octreotide
- $[^{90}\text{Y-DOTA}^0,\text{Tyr}^3]$ octreotide
- $[^{90}\text{Y-DOTA}^0]$ lanreotide
- $[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]$ octreotate
- $[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]$ octreotide
- $[^{90}\text{Y-DOTA}^0,\text{Tyr}^3]$ octreotate

Table 2: Affinity Profiles (IC(50)) for Human sst$_1$-sst$_5$ Receptors of a Series of Somatostatin Analogues

<table>
<thead>
<tr>
<th>Peptide</th>
<th>sst$_1$</th>
<th>sst$_2$</th>
<th>sst$_3$</th>
<th>sst$_4$</th>
<th>sst$_5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin-28</td>
<td>5.2 (0.3)</td>
<td>2.7 (0.3)</td>
<td>7.7 (0.9)</td>
<td>5.6 (0.4)</td>
<td>4.0 (0.3)</td>
</tr>
<tr>
<td>Octreotide</td>
<td>$&gt;10,000$</td>
<td>2.0 (0.7)</td>
<td>187 (55)</td>
<td>$&gt;1000$</td>
<td>22 (6)</td>
</tr>
<tr>
<td>DTPA-octreotide</td>
<td>$&gt;10,000$</td>
<td>12 (2)</td>
<td>376 (84)</td>
<td>$&gt;1000$</td>
<td>299 (50)</td>
</tr>
<tr>
<td>In-DTPA-octreotide</td>
<td>$&gt;10,000$</td>
<td>22 (3.6)</td>
<td>182 (13)</td>
<td>$&gt;1000$</td>
<td>237 (52)</td>
</tr>
<tr>
<td>DOTA-[Tyr$^3$]octreotide</td>
<td>$&gt;10,000$</td>
<td>14 (2.6)</td>
<td>880 (324)</td>
<td>$&gt;1000$</td>
<td>393 (84)</td>
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<tr>
<td>DOTA-[Tyr$^3$]octreotate</td>
<td>$&gt;10,000$</td>
<td>1.5 (0.4)</td>
<td>$&gt;1000$</td>
<td>453 (176)</td>
<td>547 (160)</td>
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<tr>
<td>DOTA-lanreotide</td>
<td>$&gt;10,000$</td>
<td>26 (3.4)</td>
<td>771 (229)</td>
<td>$&gt;10,000$</td>
<td>73 (12)</td>
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<tr>
<td>Y-DOTA-[Tyr$^3$]octreotide</td>
<td>$&gt;10,000$</td>
<td>11 (1.7)</td>
<td>389 (135)</td>
<td>$&gt;10,000$</td>
<td>114 (29)</td>
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<tr>
<td>Y-DOTA-[Tyr$^3$]octreotate</td>
<td>$&gt;10,000$</td>
<td>1.6 (0.4)</td>
<td>$&gt;1000$</td>
<td>523 (239)</td>
<td>187 (50)</td>
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<tr>
<td>Y-DOTA-lanreotide</td>
<td>$&gt;10,000$</td>
<td>23 (5)</td>
<td>290 (105)</td>
<td>$&gt;10,000$</td>
<td>16 (3.4)</td>
</tr>
</tbody>
</table>

All values are half-maximal inhibitory concentration (IC50) (SEM) in nM. (Adapted from Reubi JC et al. 21)
\textbf{177}Lu-DOTA-Tyr^3-Octreotate

\begin{itemize}
  \item \textbf{177}Lu
    \begin{itemize}
      \item Intense beta radiation
      \item 0.94 MeV
      \item 12 mm range
      \item T½ = 2.7 days
    \end{itemize}
  \item \textbf{111}In
    \begin{itemize}
      \item Auger electrons, gamma
      \item Cellular range 10 µm
      \item T½ = 2.8 days
    \end{itemize}
  \item \textbf{89}Y
    \begin{itemize}
      \item Mild beta radiation
      \item 0.49 MeV
      \item 2 mm range
      \item T½ 6.7 days
    \end{itemize}
\end{itemize}
Indium-111 based PRRT: 10-20% response

- Based on Auger electrons from Indium-111
  - Short therapeutic range
- Symptom relief
- Two main studies
  - Rotterdam: 5/26 decreased tumor size after 550 mCi, no PR
  - New Orleans: 2/26 PR
  - Advanced progressive patients in poor shape
  - A few cases of myelodysplasia and leukaemia
- London, Ontario combines this with chemotherapy
  - Increased survival…
    - Special access HC, no reporting
Ytrium-90 based PRRT: ~30% response

- **Basel (n=29)**
  - Phase I and II, dose escalations to 6 – 7.4 GBq/m², in 4 doses
  - Renal insufficiency in 4 / 29 without kidney protection
  - Two doses of 200 mCi: CRs and PRs 12 out of 36

- **Milan (n=21)**
  - With dosimetry, renal protection
  - MTD: based on 43% grade 3 haematological toxicity – reversible
  - No kidney failures
  - PRs and CRs in 28% out of 87 various NETs
  - 21 GEPNETs: 29% tumor regression, lasting 9 months median

- **Rotterdam results (n=58)**
  - Kidney protection, limited to 27 Gy
  - Doses up to 14.8 GBq/m², single doses max 250 mCi
  - PR in 5 = 9%
  - MR in 7 = 12%
  - Time to progression in SD, MR or PR was 30 months
Lutetium-177 DOTATate based PRRT

- Best agent

- Modifications
  - Peptide DTPA$^0$, Tyr$^3$, octreotate
  - Improved binding in animal experiments
  - With DOTA 9-fold further affinity increase
  - Doubled residence times in tumor
  - Lutetium-177: Better suited for therapeutic effect

- Uptake in kidney, spleen, liver similar to In111, but tumor uptake 4 fold higher

Figure 1 Planar anterior scintigrams 1 day after the administration of 3700 MBq (100 mCi) of $^{177}$Lu-DOTA$^0$, Tyr$^3$octreotide (left) or $^{177}$Lu-DOTA$^0$, Tyr$^3$octreotate (right) in the same patient with liver and bone metastases from GEPNETs. Note the higher uptake in the tumor sites after $^{177}$Lu-DOTA$^0$, Tyr$^3$octreotate, with similar uptake in liver and spleen. (Adapted from Esser JP et al.$^{23}$)
[¹⁷⁷Lu-DOTA⁰,Tyr³]Octreotate Therapy

Most important Inclusion Criteria

- Pathology proven, inoperable tumor
- Tumor uptake on octreoscan ≥ normal liver.
- No prior therapy with other radiolabelled somatostatin analogues.
- Hb ≥ 6 mmol/L; WBC ≥ 2*10⁹/L; Platelets ≥ 80*10⁹/L; serum creatinine ≤ 150 umol/L.
- Karnofsky Performance Status ≥ 50.
- Signed informed consent

Courtesy Dik Kwekkeboom, Erasmus Medical Center, Rotterdam, The Netherlands
[\textsuperscript{177}Lu-DOTA\textsuperscript{0},Tyr\textsuperscript{3}]Octreotate Therapy

- Kidney protection with amino acid infusion
- Maximum dose determined by radiation dose to:
  - Bone marrow (2 Gy) Max: 800 mCi
  - Kidneys (23 Gy) Individual calculation

Full patient doses 600-800 mCi in 3 – 4 sessions

Courtesy Dik Kwekkeboom, Erasmus Medical Center, Rotterdam, The Netherlands
[\textsuperscript{177}Lu-DOTA\textsuperscript{0,Tyr\textsuperscript{3}}]-Octreotate Therapy: Treatment update January 2000 - July 2006

Number of treatments: 1968
Number of patients: 562

Off Protocol: 58 patients
According to Protocol: 504 patients
Non-GEP: 46 patients
GEP: 458 patients

Courtesy Dik Kwekkeboom, Erasmus Medical Center, Rotterdam, The Netherlands
Rotterdam: Lu-177-octreotate PRRT toxicity in 504 patients (1772 administrations)

- Side effects predictable from scan
  - No effect on thyroid and pituitary
- Early toxicity
  - Nausea in 25%, vomiting in 10%, within first 24 hrs
  - Hormonal crisis 1%
  - Haematological tox grade 3 in 3.6% administrations or overall in 9.5% of patients
    - after 4-8 weeks
    - Age > 70, previous chemo, eGFR<60, bone mets predictive
  - Temporary hair loss in 62%
- Serious delayed tox in 9
  - 2 renal insufficiency (unrelated), 3 liver, MDS in 4

[177Lu-DOTA₀,Tyr³]Octreotate Therapy - example

 Courtesy Dik Kwekkeboom, Erasmus Medical Center, Rotterdam, The Netherlands
[\textsuperscript{177}Lu-DOTA\textsuperscript{0,Tyr\textsuperscript{3}}]Octreotate Therapy: Tumor Uptake and Response (MR, PR, CR)

Percentage Remission

Courtesy Dik Kwekkeboom, Erasmus Medical Center, Rotterdam, The Netherlands
[¹⁷⁷Lu-DOTA⁰,Tyr³]Octreotate Therapy in GEP Tumors: AntiTumor Effects during follow-up

3 months after last treatment; n=310
- PR 29%
- PD 20%
- MR 16%
- SD 35%

6 months; n=232
- New MR/PR 4%
- PD 6%
- Similar 3 months 90%

12 months; n=165
- New MR/PR 5%
- PD 13%
- Similar 6 months 82%

Courtesy Dik Kwekkeboom, Erasmus Medical Center, Rotterdam, The Netherlands
[\textsuperscript{177}Lu-DOTA\textsuperscript{0},Tyr\textsuperscript{3}]Octreotate Therapy: Liver metastases from a Pancreatic NET

Ongoing regression and change in appearance of liver metastases

Courtesy Dik Kwekkeboom, Erasmus Medical Center, Rotterdam, The Netherlands
[\[^{177}\text{Lu-DOTA}^0, \text{Tyr}^3\]\] Octreotate Therapy
282 GEP-NET Tumor Patients / Censored Survival

Survival and SWOG antitumor responses

Median: 11.3**

CT or MRI based !!

No distinction between Tumour / Fibrosis

NEED: Functional Imaging

Courtesy Dik Kwekkeboom, Erasmus Medical Center, Rotterdam, The Netherlands
[¹⁷⁷Lu-DOTA⁰,Tyr³]Octreotate Therapy: Comparison of survival data

Survival benefit: 40-72 months

Reference Studies:
3. Update 2. Oberg; personal comm 2007
5. Mazzaglia et al.; Surgery 2007
Rotterdam: Lu-177-octreotate PRRT

- CR, PR, MR together 46%
- Factors: scan uptake, performance score, liver
- Limited side effects
- Long time to progression: median 40 months
- Median overall survival: 46 months
- Survival increase since diagnosis: 40–72 months
  - Compared to historical controls
- Improved QoL

- No randomised trials
- Need for standardisation diagnosis, treatment, follow-up
- No survival difference between PR, MR and SD
- Single center
LuMark
GMP produced Lutetium-177\(^{177}\text{Lu}\)
Radiopharmaceutical precursor

- Specific activity > 740\,GBq/mg
- Weekly availability
- Shipping worldwide
Others doing PRRT: similar

There is a lack of good publications
Chemotherapy: slightly worse

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Tumor Types</th>
<th>No of Patient</th>
<th>PR/CR (%)</th>
<th>Median PFS (mo)</th>
<th>Median OS (Mo)</th>
<th>Study (yr)</th>
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<tbody>
<tr>
<td>STZ + Doxorubicin</td>
<td>PNET</td>
<td>16</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>Cheng and Saltz⁴¹</td>
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<td>Dacarbazine</td>
<td>Carc</td>
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<td>16</td>
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<td>7</td>
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<td>Andreyev et al³⁹</td>
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<td>Ansell et al⁴²</td>
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<td>STZ + FU + Doxorubicin</td>
<td>PNET</td>
<td>84</td>
<td>39</td>
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<td>Kouvaraki et al⁴⁷</td>
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<td>Carc</td>
<td>85</td>
<td>13</td>
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<td>Sun et al⁴³</td>
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<td>STZ + FU</td>
<td>Carc</td>
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<td>15</td>
<td>5</td>
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<td>Oxaliplatin + Capecitabine</td>
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<td>⁴⁷¹Lu-octreotide</td>
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<td>30</td>
<td>32</td>
<td>46</td>
<td>Kwekkeboom et al¹³</td>
</tr>
</tbody>
</table>

STZ, streptozotocin; FU, 5-fluorouracil; IF-A, interferon-alpha; PNET, pancreatic neuroendocrine tumor; Carc, carcinoid; PFS, progression-free survival; OS, overall survival; NA, not available. (Adapted from Kwekkeboom DJ et al.¹³)
Novel drugs - preliminary

- Capecitabine PR 12/17, SD 5/17
- Bevacizumab PR 14%, SD 79%
- Sorafenib 17% responses
- Imatinib 1 PR, 17 SD
- Sunitinib PR 17%, n = 66
- Everolimus PR 17%, n = 60
  - n=60, 39 wit PD at entry
$^{18}$F-DOPA: born at McMaster*

FACILITIES
- SIEMENS 11 MeV CYCLOTRON
- ESTABLISHMENT LICENCE
- GMP LABORATORY
- SMALL ANIMAL PET AND SPECT
- ANIMAL QUARTER

Fathers: Steve Garnett, Gunter Firnau, Raman Chirakal et al.
NE tumors and Canada

- This is not a rare disease
- Some patients feel lost
- More knowledge, interest, attention would help
- Better diagnostic tools would help
  - 18F-DOPA PET within reach
    - Subgroups: carcinoid, MTC, phaeo, hyperinsulinism
  - 68Ga-peptide PET?
    - Better in other subgroups
- More treatment choices would help
Thank you for your attention